Diabetes Is an Independent Predictor for Severe Osteoarthritis

Results from a longitudinal cohort study

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OBJECTIVE—To evaluate if type 2 diabetes is an independent risk predictor for severe osteoarthritis (OA).

RESEARCH DESIGN AND METHODS—Population-based cohort study with an age- and sex-stratified random sample of 927 men and women aged 40–80 years and followed over 20 years (1990–2010).

RESULTS—Rates of arthroplasty (95% CI) were 17.7 (9.4–30.2) per 1,000 person-years in patients with type 2 diabetes and 5.3 (4.1–6.6) per 1,000 person-years in those without ($P < 0.001$). Type 2 diabetes emerged as an independent risk predictor for arthroplasty: hazard ratios (95% CI), 3.8 (2.1–6.8) ($P < 0.001$) in an unadjusted analysis and 2.1 (1.1–3.8) ($P = 0.023$) after adjustment for age, BMI, and other risk factors for OA. The probability of arthroplasty increased with disease duration of type 2 diabetes and applied to men and women, as well as subgroups according to age and BMI. Our findings were corroborated in cross-sectional evaluation by more severe clinical symptoms of OA and structural joint changes in subjects with type 2 diabetes compared with those without type 2 diabetes.

CONCLUSIONS—Type 2 diabetes predicts the development of severe OA independent of age and BMI. Our findings strengthen the concept of a strong metabolic component in the pathogenesis of OA.

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Osteoarthritis (OA) is among the most frequent chronic diseases in the industrialized world, with estimation for the lifetime prevalence ranging from 30–50% (1,2). Moreover, OA is associated with a substantial disease burden due to pain, functional decline and increased mortality (2). In a proportion of individuals, OA progresses toward joint failure requiring total joint replacement (arthroplasty). In the U.S., 200,000 hip joints are replaced every year, and intervention rates for hip and knee OA are between 50 to 130 per 100,000 person-years in most Western countries (3). Relevancy of OA for public health will further increase owing to the incremental ageing and overnutrition (4). OA already constitutes a major source of morbidity and is considered as driving force of health costs in aged populations next to cardiovascular disease, type 2 diabetes, and dementia.

Despite the striking impact of OA, its etiopathogenesis is still poorly defined, with limited experimental insights into disease mechanisms and the underlying risk factors. It is well established, however, that OA shares similarities with type 2 diabetes, including its chronic nature, high prevalence of end-organ failure, and strong association with age and obesity (5–7). Whether type 2 diabetes represents a causal risk factor for OA remains unclear to date (8). Metabolic factors are important for the development of OA as suggested by several lines of evidence: *1*) The association between obesity and OA extends beyond weight-bearing joints, suggesting that this link is not solely based on mechanical factors (9). *2*) Metabolic syndrome is significantly more common among subjects with than without OA (10,11). In accordance, fasting glucose levels are higher in OA patients than in non-OA controls (11,12). *3*) Finally, a small cross-sectional study from the 1960s (13) showed higher prevalence of radiographic OA in diabetic subjects than in nondiabetic individuals and a later evaluation on radiographic hip OA in patients receiving hip arthroplasty showed a surplus of bilateral joint involvement in diabetic patients (13,14).

In this study, we hypothesize that type 2 diabetes indeed represents an independent risk factor for the development of severe OA. We thus investigated the risk for arthroplasty, as well as clinical symptoms and imaging signs of OA in diabetic and nondiabetic subjects included in the long-term population-based Bruneck Study.

RESEARCH DESIGN AND METHODS

Characteristics of the Bruneck Study

The Bruneck cohort is a prospective population-based study on the epidemiology and pathogenesis of cardiovascular, neurologic, and musculoskeletal diseases (15–17), which has already been used to define the impact of type 2 diabetes on cardiovascular disease (18,19). This cohort is characterized by unique homogenous

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access to one public health care system, represented by the Bruneck Hospital, which is the only health care provider in the entire region. Thus, all medical records of each individual were collected and completely accessible in the same place, minimizing bias due to incomplete medical information.

Patients

The study population was recruited in 1990 (baseline) as a random sample (n = 1,000), stratified according to sex and age, of all inhabitants of Bruneck (125 women and 125 men in each of the fifth to eighth decades of age). A total of 927 men and women were enrolled and followed until 2010, with examinations conducted every 5 years (1990, 1995, 2000, 2005, and 2010) and participation rates >90%. Population mobility within the Bruneck area was low at 0.2% per year and migration to outside communities was a rare event (n = 4 during the 20 years of follow-up). We succeeded to trace all of these few individuals, who participated in the follow-up exam or provided access to their medical records.

Data on type 2 diabetes and arthroplasty were available in all 927 subjects, including 576 subjects who were alive in 2010 and 351 subjects who died during the 20 years of follow-up. The study protocol of the Bruneck Study was reviewed and approved by the ethics committees of Bolzano and Verona, and all study subjects gave their written informed consent.

Baseline and follow-up examinations

At baseline and each 5-year follow-up, demographic and socioeconomic characteristics, comorbidities, and medication (including antidiabetic treatment, analgesic, and nonsteroidal anti-inflammatory drugs) were recorded. Assessment of comorbidities included cardiovascular disease (angina, myocardial infarction, heart failure, claudication, and stroke), cancer, chronic obstructive pulmonary disease (including asthma, bronchitis, and emphysema), arterial hypertension, chronic inflammatory disease, and neuropsychiatric disorders. Data were retrieved from *1*) clinical history taking and medical record review; *2*) complete physical and neurologic examination; and *3*) measures such as blood pressure recording, electrocardiography, and carotid ultrasonography. Polyneuropathy was ascertained by a thorough clinical examination conducted by an experienced senior neurologist and graded as mild (sub- or preclinical disease), moderate (manifest sensory and/or motor deficits), or severe (disabling disease with severe impairment of gait).

Ascertainment of type 2 diabetes

Presence of type 2 diabetes was diagnosed according to the classic American Diabetes Association criteria (fasting glucose ≥7 mmol/L [126 mg/dL] or a clinical diagnosis of type 2 diabetes with ongoing antidiabetic treatment) (20). In a sensitivity analysis, the most recent diagnostic criteria were applied (fasting glucose ≥7 mmol/L [126 mg/dL] or a clinical diagnosis of type 2 diabetes with ongoing antidiabetic treatment or HbA_{1c} levels ≥6.5% or 2-h glucose level ≥11.1 mmol/L [200 mg/dL] after a standard 75-g glucose load) (21). The BMI was calculated as weight divided by height squared (kg/m^2). Smoking status and alcohol consumption were recorded as detailed previously (15–17). Physical activity was recorded by composed score for work (three categories) and sports/leisure activities (0, ≤2, and >2 h per week) (15–17). Socioeconomic status was categorized on a three-category scale (low, medium, and high) based on information about occupational status and educational level of the person with the highest income in the household (15–17). Blood samples were drawn after an overnight fast and abstinence from smoking. Total cholesterol, HDL cholesterol, uric acid, creatinine, ferritin, and high-sensitivity C-reactive protein were all assessed by standard methods (15–17). LDL cholesterol was calculated with the Friedewald formula except for patients with a triglyceride level >400 mg/dL. Vascular cellular adhesion molecule (VCAM)-1 was detected by enzyme-linked immunosorbent assay (17).

Longitudinal assessment of arthroplasty between 1990 and 2010

Localization, date, and circumstances of total hip and knee arthroplasty occurring between 1990 and 2010 were carefully recorded using three sources of information: subject self-report, medical records of the Bruneck Hospital and general practitioners, and a standardized evaluation of all radiographs ever taken on study subjects. Arthroplasty following bone fractures (documented by radiographs) was not considered in the current analysis. All subjects with arthroplasty had radiographically documented OA of the hip or knee joint in at least two sequential radiographs (Kellgren-Lawrence score of at least one) before surgery and met the criteria for the diagnosis of OA (22,23). Two independent readers (R.L. and C.P.) unaware of the status of diabetes assessed the radiographs.

Cross-sectional clinical assessment of OA in 2010

In the 2010 follow-up exam, a total of 576 individuals were still alive and had full information on arthroplasty and of these, 488 participated in fourth follow-up. The self-administered questionnaires of the Knee Injury and Osteoarthritis Outcome Score (KOOS) and the Western Ontario and McMaster University Osteoarthritis Index (WOMAC), both addressing the severity of symptoms (pain, stiffness, and joint function) associated with OA, were filled out by 347 men and women who did not differ from the overall group of 488 participants in any of the population characteristics assessed.

Cross-sectional imaging assessment of OA in 2010

In order to evaluate the severity of knee OA, bilateral ultrasound (US) examination of the knee joints was performed by an independent experienced examiner blinded to clinical symptoms and presence of laboratory or radiographic abnormalities in 443 individuals (90.8%) (24–26). The US exam was performed by a single reader (C.P.) using an ESAOTE MyLab25 US system (Esaote Biomedica, Genoa, Italy) equipped with a broadband 4–13 MHz linear transducer for US examination. Both transverse and longitudinal scans of the supra-and infrapatellar region and the lateral and medial recesses were performed. Presence of synovitis (i.e., hypoechoic synovial hypertrophy and joint effusion according to the Outcome Measures in Rheumatology definition) in grayscale and power Doppler signal in the synovial membrane (settings: pulse repetition frequency 750 Hz, gain 40–50 dB) were recorded in each compartment. Presence of grayscale synovial hypertrophy and joint effusion as well as Doppler signal was recorded according to a semiquantitative scale (0 = normal; 1 = mild change; 2 = moderate change; 3 = severe change). The summed total score of inflammatory-related abnormalities (effusion, synovial hypertrophy, and power Doppler signal) was also calculated (range from 0–9 in each joint).

Statistical analysis

Data were analyzed using the statistical packages SPSS version 18.0 (SPSS) and STATA version 10.1 (StataCorp). For computation of intervention rates, person-years

of follow-up for each participant were accrued from the 1990 baseline until arthroplasty, age 90 years, death, or 1 October 2010, whichever came first. Cox proportional hazard models were fitted to assess the association between baseline type 2 diabetes and arthroplasty due to severe OA during follow-up. The proportional hazard assumption was confirmed for type 2 diabetes by testing the interaction of type 2 diabetes with a function of survival time (Cox model with time-dependent covariates). When the exact date of arthroplasty was not available, we used the date of the first X ray showing the implant as a surrogate. This may be viewed as an adequate approximation in most individuals and, if at all, errs on the conservative side. The base model was unadjusted, whereas multivariable models were adjusted for established predictors of severe OA [age, sex, prior arthroplasty, BMI, and $\log_e$-transformed level of soluble VCAM-1 (17); model 1] and, additionally, for social class, smoking, alcohol consumption, physical activity score, and levels of uric acid, creatinine, LDL cholesterol, $\log_e$-transformed high-sensitivity C-reactive protein (hsCRP), and ferritin (model 2). Differential effects of type 2 diabetes on the probability of arthroplasty in subgroups according to age, sex, and BMI were tested by inclusion of appropriate interaction terms. Sensitivity analyses with an update of key variable (diabetes status and BMI) were fitted using Cox regression analysis with time-dependent covariates in order to control for switches in diabetes status and for weight gain during follow-up. Comparison of US measures and clinical score levels between subjects with and without type 2 diabetes (2010) was performed with the *t* test and χ^2 test (for trend in case of more than two categories) and, in a multivariable setting, with unconditional logistic regression analysis and general linear models. All reported *P* values were two-sided.

RESULTS

Prospective analysis of arthroplasty in subjects with and without type 2 diabetes in the Bruneck Study (1990–2010)

At baseline, 69 of the 927 participants of the Bruneck Study met the diagnostic criteria for type 2 diabetes. Mean HbA_{1c} at baseline was 7.2%. Oral antidiabetic drugs were used in 41 and insulin in 3 of the 69 participants. A total of 31 of the 69 patients with diabetes (44.9%) had clinical signs of a polyneuropathy at baseline (mild, 20; moderate, 11; severe, 0), and this proportion increased to 55.1% during follow-up (mild, 22; moderate, 16; severe, 0). No subjects had been affected by type 1 diabetes. Baseline characteristics of diabetic and nondiabetic subjects are summarized in Table 1.

Between 1990 and 2010, 13 arthroplasties due to severe symptomatic hip/knee OA were performed in diabetic subjects corresponding to an intervention rate (95% CI) of 17.7 (9.4–30.2) per 1,000 person-years. During the same period, 73 interventions were done in the nondiabetic group corresponding to an intervention rate (95% CI) of 5.3 (4.1–6.6) per 1,000 person-years. In unadjusted Cox models, the hazard ratio (HR) (95% CI) of joint failure for type 2 diabetes was 3.8 (2.1–6.8) ($P < 0.001$) (Table 2). Remarkably, type 2 diabetes remained a significant predictor of arthroplasty after controlling for a variety of other putative risk factors for OA including age and BMI (HR [95% CI], 2.1 [1.1–3.8]; $P = 0.023$). To account for weight gain during follow-up (e.g., related to insulin treatment), BMI was updated every 5 years during follow-up from 1990–2010 (Table 2). This sensitivity analysis yielded similar risk estimates for type 2 diabetes (HR [95% CI], 2.2 [1.2–4.1]; $P = 0.013$). Several further sensitivity analyses with an update of diabetes status during follow-up or application of the most recent American Diabetes association definition of diabetes (21) yielded very similar results (Table 2). Findings were also consistent when additionally adjusting the analysis for lifestyle factors including smoking and physical activity and serum parameters such as CRP (HR [95% CI], 2.1 [1.1–4.0]; $P = 0.026$) (Table 2). Moreover, results were similar in men and women and subgroups according age and BMI (*P* values for interaction: 0.421, 0.844, and 0.192). Of note, severity of OA, as assessed by the Kellgren-Lawrence score (range 0–10 points) in the last radiograph prior to arthroplasty, was similar in subjects with and without type 2 diabetes (mean ± SD: 5.5 ± 1.7 vs. 5.8 ± 1.6 points, both values resembling severe radiographic Kellgren-Lawrence stage 3 OA; $P = 0.84$), as was the mean age at surgery (74.1 vs. 72.6 years; $P = 0.35$).

In the cumulative hazard plot (Fig. 1), the lines for diabetic and nondiabetic subjects diverged over time, indicating relevance of disease duration for the manifestation of severe OA. Mean time between diagnosis of type 2 diabetes and joint failure necessitating surgical intervention was 10.7 years in our cohort. In line, type 2 diabetes disease duration was

Table 1—*Baseline demographic, lifestyle, and laboratory characteristics in subjects with and without type 2 diabetes* (n = 927)

	Type 2 diabetes		
Characteristic*	No (*n* = 858)	Yes (*n* = 69)	*P* value†
Age (years)	58.2 ± 11.3	67.6 ± 9.6	<0.001
Male sex (%)	50.3	49.7	0.451
BMI (kg/m^2)	24.8 ± 3.7	27.0 ± 3.9	<0.001
Social status (%)			
Low	61.4	75.4	0.923
Medium	21.7	7.2	
High	16.93	17.4	
sVCAM-1 (ng/mL)	609.2 (491.8–789.7)	736.9 (600.9–876.7)	0.036
Smoking (%)	24.7	18.8	0.636
Alcohol consumption (g/day)	30.8 ± 40.6	36.56 ± 49.0	0.385
Physical activity (score)	4.4 ± 1.5	3.6 ± 1.6	0.011
Uric acid (μmol/L)	315.2 ± 83.3	368.8 ± 113.0	0.005
Creatinine (μmol/L)	69.8 ± 36.2	71.4 ± 15.0	0.853
LDL cholesterol (mmol/L)	3.56 ± 0.98	3.78 ± 1.09	0.147
hsCRP (mg/L)	1.4 (0.8–5.7)	3.1 (1.4–8.0)	0.001
Ferritin (pmol/L)	318.8 ± 340.6	613.4 ± 783.5	<0.001

sVCAM-1, soluble VCAM-1. *Values presented are means ± SD, median (interquartile range), or percentages. Factors to convert Système International units into conventional units are as follows: LDL cholesterol, 0.02586; and creatinine, 88.4. †*P* values for the variables age and sex are from unadjusted analyses. All other *P* values are from logistic regression models adjusted for age and sex. For computation of *P* values, CRP and sVCAM levels were $\log_e$-transformed because of a markedly skewed distribution.

Table 2—*Prospective association of type 2 diabetes with severe OA requiring joint arthroplasty during 20 years of follow-up (Bruneck Study 1990–2010,* n = 927)

	Participants without type 2 diabetes (*n* = 858)	Participants with type 2 diabetes (*n* = 69)	*P* value
Arthroplasty			
No. of cases	73	13	
Person-years of follow-up	13,835	735	
Intervention rate per 1,000 person-years	5.3 (4.1–6.6)	17.7 (9.4–30.2)	
Cox models [HR (95% CI)]			
Unadjusted	1 (Reference)	3.76 (2.07–6.81)	<0.001
Multivariable model 1[a]	1 (Reference)	2.06 (1.11–3.84)	0.023
Multivariable model 1[a,b]	1 (Reference)	2.20 (1.19–4.09)	0.013
Multivariable model 1[a,c]	1 (Reference)	1.72 (1.01–2.93)	0.045
Multivariable model 1[a,d]	1 (Reference)	2.19 (1.27–3.80)	0.005
Multivariable model 1[a,e]	1 (Reference)	1.81 (1.00–3.26)	0.049
Multivariable model 2[f]	1 (Reference)	2.08 (1.09–3.95)	0.026
Multivariable model 2[f,g]	1 (Reference)	2.09 (1.10–3.99)	0.025

HR and 95% CI were derived from Cox regression analysis. Participants with arthroplasty and those turning 90 years of age were censored for subsequent follow-up. [a]Adjusted for age, sex, prior joint replacement, BMI, and $\log_e$-transformed level of soluble VCAM-1. [b]In this analysis, baseline BMI was updated every 5 years (Cox regression analysis with time-dependent covariate) to account for weight gain (e.g., related to insulin treatment). [c]In this analysis, baseline diabetes status was continuously updated during the 20-year follow-up period (Cox regression analysis with time-dependent covariate). [d]In this analysis, baseline diabetes status was continuously updated during the first 10-year follow-up period (Cox regression analysis with time-dependent covariate). This approach ensures adequate exposure time for severe OA to emerge and considers the fact that the average time interval between diagnosis of diabetes and arthroplasty was >10 years in our study. [e]In this analysis, the most recent diagnostic criteria for type 2 diabetes of the American Diabetes Association were applied (see RESEARCH DESIGN AND METHODS; *n* = 93 at baseline). [f]Adjusted for everything in footnote [a] and for social class, smoking, alcohol consumption, physical activity score, and levels of uric acid, creatinine, LDL cholesterol, $\log_e$-transformed hsCRP, and ferritin. [g]Six subjects with arthroplasty due to severe OA prior to baseline (1990) were excluded.

significantly higher in diabetic patients with arthroplasty than in those without arthroplasty (Fig. 1).

Subjects with impaired fasting glucose at baseline (1990, *n* = 86) showed a moderately elevated risk of arthroplasty due to severe OA (unadjusted HR [95% CI], 2.0 [1.1–3.7]; *P* = 0.030), which lost significance in the multivariable model (HR [95% CI], 1.6 [0.9–3.0]; *P* = 0.145).

Cross-sectional analysis of OA in diabetic and nondiabetic subjects in 2010

On a cross-section (2010), patients with prevalent diabetes (*n* = 74) were more likely to have received replacement of knee and hip joint (implanted for alleviation of OA symptoms) than nondiabetic individuals (knee arthroplasty, intervention proportion 10.8 vs. 3.3%, *P* = 0.006; hip arthroplasty, intervention proportion 9.5 vs. 5.0%, *P* = 0.167). To further elaborate the association between type 2 diabetes and OA, a number of ancillary cross-sectional analyses were performed. Evaluation of the clinical symptoms of OA by total WOMAC score, a validated patient-related measure of signs and symptoms of OA, showed significantly more severe OA symptoms in subjects with type 2 diabetes than in controls (Table 3). Results were consistent in unadjusted (*P* = 0.034) and fully adjusted models (*P* = 0.030). Moreover, WOMAC subscales for joint pain and function were lower (i.e., more pathologic in type 2 diabetic patients than controls) (*P* values from multivariable analyses 0.014 and 0.004; Table 3). Finally, results were replicated when applying another validated score for the quantification of clinical disease activity in OA, the KOOS questionnaire (pain score, *P* value from multivariable analyses 0.001; Table 3).

We performed examinations of knee joints by US in 443 individuals of the Bruneck Study population in 2010 (90.8%), searching for signs of inflammation including synovitis and joint effusion. Subjects without US data (*n* = 55) were more likely to be female and diabetic but otherwise similar to the entire population. Bilateral joint effusion was found in 51.1% of subjects with type 2 diabetes but only in 30.9% of the subjects without type 2 diabetes (Table 3). In accordance, uni- and bilateral signs of synovitis in the knee joints were significantly more frequent in diabetic than nondiabetic subjects (*P* value from multivariable analyses 0.004; Table 3). Data were consistent when focusing on both synovitis and effusion in a single model (*P* value from multivariable analyses 0.003; Table 3). Finally, severity of synovitis as quantified by the synovitis score was more pronounced among patients with type 2 diabetes (Table 2).

CONCLUSIONS—To our best knowledge, this is the first time that it was shown that diabetes can be considered as an independent predictor of severe OA necessitating joint arthroplasty. OA is a major challenge to health in the industrialized world. *1*) Its prevalence is high and further increases due to ageing of the populations. *2*) Furthermore, its impact on quality of life is substantial due to an impairment of locomotor function and decrease in functional capacities. *3*) Finally, its conservative treatment options are limited, and surgical replacement of damaged joints may be necessary in severe cases. Therefore, definition of risk predictors for OA is of key importance, particularly if these risk factors can be modified by either lifestyle changes or medications. In this study, we show that long-standing type 2 diabetes is independently associated with advanced OA of knee and hip joints. This finding adds to the yet short list of risk predictors for OA established in prospective evaluations (5,6,17). After controlling the analysis for age, BMI, and other potential confounders, type 2 diabetes comprised a twofold risk of severe OA necessitating arthroplasty.

The population-based design is a strength of this study (27,28), as well as its long-term and complete follow-up and the use of joint failure necessitating arthroplasty as a hard end point. A further strength of our study is that the link between type 2 diabetes and OA was consistent when using three distinct approaches of OA ascertainment as follows: *1*) joint failure as determined by arthroplasty; *2*) signs and symptoms of OA as quantified by the WOMAC and KOOS scores; and *3*) severity of joint changes as determined by musculoskeletal US.

The moderate number of arthroplasties (<100) can be considered as a limitation of study. However, this is not surprising because arthroplasty accomplishes the most

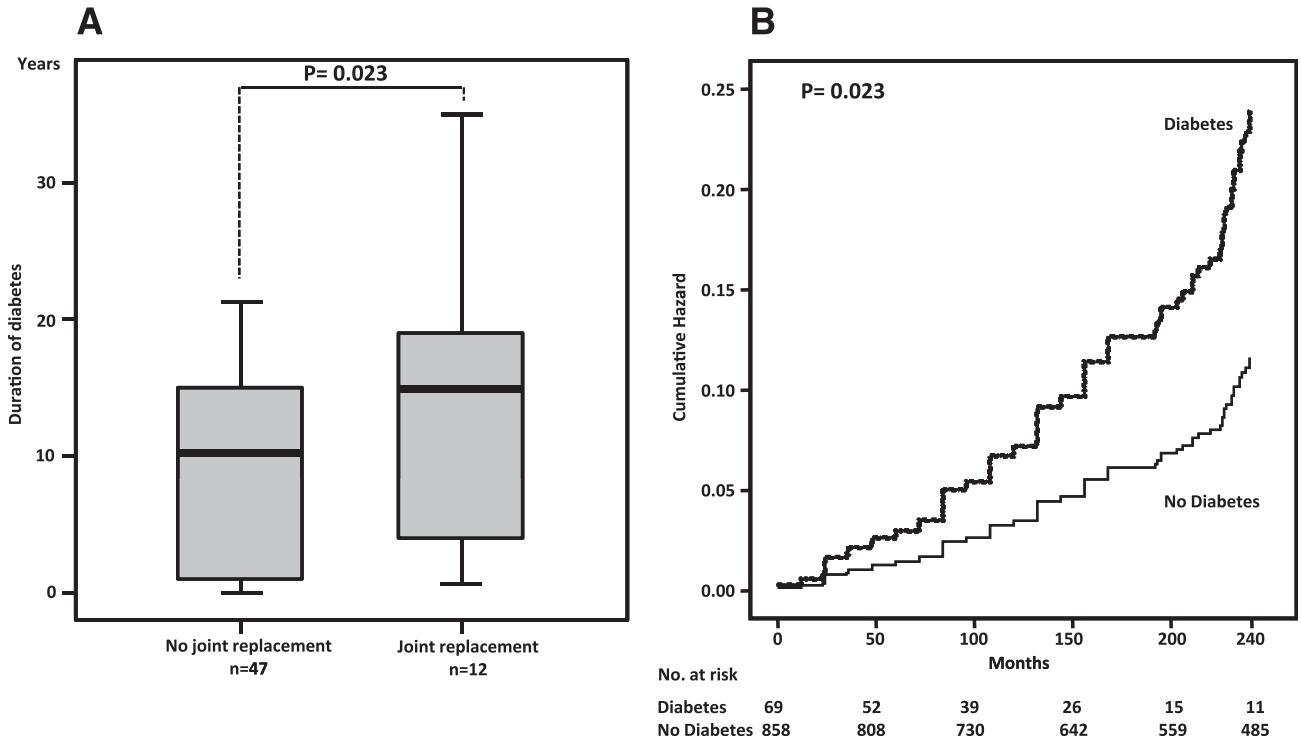

Figure 1—A: *Disease duration of type 2 diabetes in diabetic patients with and without arthroplasty due to severe OA.* B: *Cumulative hazard curves for total knee and hip arthroplasty (OA) by type 2 diabetes status, 1990–2010* (n = *927*) (P = *0.023*).

severe disease phenotype of OA, which is less prevalent. Moreover, results from our study launched in a small town, in which accessibility to health resources is very high, are not necessarily representative for other Western populations and await confirmation in independent studies. Also, we cannot exclude different decision-making for arthroplasty in diabetic versus nondiabetic subjects. Subjects with diabetes may receive more medical attention than nondiabetic individuals, leading to increased awareness of or even overtreatment of OA. Moreover, fear of deterioration of the general medical condition in diabetic subjects could, at least theoretically, lead to earlier interventions in this group. In contrast, studies showing a higher risk of complications and of revisions of arthroplasty in diabetic subjects could translate into a more conservative indication for surgical interventions resulting in an underestimation rather than overestimation of the effect size of diabetes in our study (29). Actually, in the current study, radiographic severity of OA prior to surgery (Kellgren-Lawrence score) and the age at arthroplasty both were identical in subjects with and without type 2 diabetes, suggesting no major differences in the indication for interventions in these groups.

The link between obesity and OA is well-established and particularly supported by longitudinal data showing that obesity entails a higher risk for developing severe OA (6). Traditionally, mechanical factors have been considered to explain more rapid joint degeneration in obese individuals. However, this concept has been challenged by the link between obesity and OA in non–weight-bearing joints, suggesting that metabolic changes directly enhance the risk of OA. Despite evidence from cross-sectional studies that OA is linked to the metabolic syndrome and higher blood glucose levels (10–12), no study addressed whether diabetes is independently linked to OA and in particular whether such a link is independent of body weight. Our study is the first to show that type 2 diabetes predicts severe OA independent of age, sex, and BMI and provides both longitudinal and cross-sectional evidence for an independent association between type 2 diabetes and OA.

Moreover, several lines of experimental evidence may help to explain the link between type 2 diabetes and OA: *1*) chondrocytes express the GLUT/SLC2A, and high blood glucose levels shift the synthesis pattern of chondrocytes from type II collagen to reactive oxygen species, potentially mediating cartilage destruction (30–32). *2*) Advanced glycosylation end products elicited by sustained hyperglycemia can stimulate chondrocyte expression of proinflammatory and prodegenerative proteins via the receptor for advanced glycosylation end products (33–35). In this context, it is worth mentioning that elevated circulating levels of interleukin-6 and tumor necrosis factor-α have recently been demonstrated in patients with knee OA (36). Moreover, our data from knee US showed that signs of inflammation are more frequent and severe in the joints of diabetic subjects than nondiabetic individuals. *3*) Finally, sensory and motor polyneuropathy is a common complication of type 2 diabetes and may increase the risk of OA by muscle weakness and loss of vibratory sense (37) with subsequent inappropriate use of the affected joint due to altered mechanical stress forces. In this context, it is noteworthy that the pain subscales of the WOMAC and KOOS scores exhibit particularly pronounced associations with type 2 diabetes (Table 2). Sensory polyneuropathy obviously does not offset the high burden of pain in OA among diabetic subjects, rendering this potential link even more robust.

Our study fosters the concept that OA is part of the metabolic syndrome. This

Table 3—*Cross-sectional association of type 2 diabetes with clinical scores (WOMAC Osteoarthritis Index and KOOS) and US measures of knee OA (Bruneck Study 2010)*

	Participants without type 2 diabetes (n = 304)	Participants with type 2 diabetes (n = 43)	P value[a]	P value[b]
WOMAC and KOOS (n = 347)[c] [median (IQR)]				
KOOS Pain Score	97.2 (88.9–100)	91.7 (69.4–100)	0.001	0.001
KOOS Symptoms Score	96.4 (85.7–100)	89.3 (78.6–100)	0.211	0.160
WOMAC Pain	100 (90.0–100)	95.0 (77.5–100)	0.011	0.014
WOMAC Stiffness	100 (75.0–100)	100 (62.5–100)	0.495	0.603
WOMAC Function[d]	98.5 (90.9–100)	94.1 (79.4–100)	0.005	0.004
WOMAC Total Score	97.8 (89.6–100)	93.8 (79.2–100)	0.034	0.030
Joint ultrasonography (n = 438)[c]	n = 391	n = 47		
Effusion				
No [n (%)]	138 (35.3)	7 (14.9)	0.001	0.007
Unilateral [n (%)]	132 (33.8)	16 (34.0)		
Bilateral [n (%)]	121 (30.9)	24 (51.1)		
Synovitis				
No [n (%)]	209 (53.5)	13 (27.7)	< 0.001	0.004
Unilateral [n (%)]	112 (28.6)	17 (36.2)		
Bilateral [n (%)]	70 (17.9)	17 (36.2)		
Effusion and synovitis				
Neither criterion [n (%)]	133 (34.0)	6 (12.8)	< 0.001	0.003
All other [n (%)]	193 (49.4)	25 (53.2)		
Both criteria in both knees [n (%)]	65 (16.6)	16 (34.0)		
Synovitis Score [median (IQR)]	2 (0–4)	3 (0–6)	0.003	0.016

A total of 488 individuals participated in the 2010 follow-up exam, and a random subsample of 347 completed the KOOS questionnaire including the WOMAC Osteoarthritis Index. Specific subscores were calculated as follows: KOOS Activities of Daily Living Score, Pain Score, and Other Symptoms Score, WOMAC Pain Score, Stiffness Score, and Function Score. All scores were transformed to a scale of 0–100, with higher values indicating better function and fewer symptoms, respectively. Knee US was performed in a representative subsample of 443 individuals and focused on effusion and synovitis. A US synovitis score was calculated and had a range of 0–20. Five subjects with rheumatoid or psoriatic arthritis of the knee joints were excluded, leaving 438 for the current analysis. [a]P values from unadjusted analyses (t test and χ^2 test [for trend in case of more than two categories]/Fisher exact test). Clinical scores were $\log_e$-transformed for computation to approximate a normal distribution. [b]P values from adjusted analyses (general linear models and logistic regression analysis). Adjustment was performed for age, sex, BMI, social class, smoking, alcohol consumption, physical activity score, and levels of uric acid, creatinine, LDL cholesterol, $\log_e$-transformed hsCRP, and ferritin. Clinical scores were $\log_e$-transformed for computation to approximate a normal distribution. [c]Effusion and synovitis was coded present in case of previous arthroplasty due to severe OA. Supplementary analyses that exclude subjects with previous total knee replacement yielded virtually identical results. The target variable effusion and synovitis differentiates three categories: *1*) neither effusion nor synovitis in both knees; 2) both effusion and synovitis in both knees; and 3) all other. [d]The WOMAC Function Score is identical to the KOOS Activities of Daily Living Score.

notion shifts the traditional perception of OA as a degenerative joint disease based on continuous mechanical overload to a metabolic etiopathogenesis. The link between OA and type 2 diabetes suggests that alterations in glucose metabolism directly affect joint integrity independently of body weight and creates room for hope that adequate control of glucose metabolism hampers development of OA. Our findings may thus add a novel, modifiable, and highly prevalent risk condition for the development of OA.

In summary, our data show that type 2 diabetes is a strong predictor for the development of severe OA. This finding is independent of age and BMI and suggests that longstanding diabetes per se is detrimental for knee and hip joints, leading to progressive destruction and joint failure.

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